I. REACTIONS OF 4-QUINAZOLONE WITH COMPOUNDS CONTAINING THE AMINE FUNCTION

II. STUDY OF THE CLEMMENSEN REDUCTION OF SIX-MEMBERED CYCLIC AMINES CONTAINING THE KETONE FUNCTION

BY

WILLIAM VANCE RUYLE

A.B., University of Nebraska, 1942
M.A., University of Nebraska, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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PART ONE

REACTIONS OF 4-QUINAZOLONE WITH COMPOUNDS CONTAINING THE AMINE FUNCTION

Introduction

Leonard and Curtin (1) showed that 4-quinazolone reacts with primary alkylamines to give 3-alkyl-4-quinazolones. Earlier work by Kunckell (2) and by Cairncross and Bogert (3) had shown that certain 4-quinazolones and benzoylene ureas react with hydrazine hydrate to give the corresponding 3-amino compounds.

It was the purpose of this investigation to ascertain the generality of the reaction of 4-quinazolone with various amine functions and to determine the order in which the different 3-N-R groops in 3-substituted 4-quinazolones were capable of being replaced. The reaction of 4-quinazolone with secondary aliphatic amines was studied for the purpose of demonstrating that cleavage of the heterocyclic ring occurred.

Discussion Of Results

The reactions of 4-quinazolones with primary and secondary alkylamines proceeded quite slowly, if at all, even under rather vigorous conditions. In most cases at least part of the original quinazolone was recovered. With hydrazine hydrate the reactions were much faster. In reactions of 3-substituted 4-quinazolones with various amines it has been established that the order of replacement at the 3-position is NH, NC_6H_5, $\left\{\begin{matrix}NNH_2\\NC_4H_9\end{matrix}\right\}$, wherein each group can replace the one (or two) preceeding.

In the reaction of dry piperidine with 4-quinazolone, the product was shown probably to be N-(*o*-1-piperidylformiminobenzoyl)piperidine. With piperidine or morpholine which contained a small amount of water, the products were N-

(2-aminobenzoyl) piperidine and N-(2-aminobenzoyl) morpholine respectively.

It was found that 2-methyl-4-quinazolone was even less reactive toward amines than 4-quinazolone. It could not be made to react with butylamine or piperidine, but reacted with aniline and with hydrazine hydrate to give the expected 3-substituted products.

In an extension of the Niementowski reaction it was found possible to synthesize 1-methyl-4-quinazolone by reaction of formamide with N-methylanthranilic acid, and 3-butyl-4-quinazolone by reaction of formamide with N-(2-aminobenzoyl) butylamine.

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PART II

STUDY OF THE CLEMMENSEN REDUCTION OF SIX-MEMBERED CYCLIC AMINES CONTAINING THE KETONE FUNCTION

Introduction

It has been demonstrated (1,2,3) that a rearrangement of the ring structure occurs in the Clemmensen reduction of 1-ketooctahydropyridocoline. The product, 1-*aza*bicyclo-[5,3,0]decane, has been synthesized unequivocally (1), but

the manner in which rearrangement occurred has not been proved.

In this investigation we sought to determine whether the closely analogous monocyclic aminoketone, 1-methyl-2-ethyl-3-piperidone, would undergo a similar rearrangement during Clemmensen reduction.

At least two mechanisms for the rearrangement appear worthy of consideration. Prelog (1) proposed that ring opening occurred by hydrogenolysis of the bond between nitrogen and the *alpha* carbon, followed by ring closure involving the now secondary amino group and the carbonyl group. Another mechanism might involve reduction of the ketone to the carbinol or chloride, which could be precursors to an ethyleneimmonium intermediate of the type proposed by Fuson and Zirkle (4) in the rearrangement of 1-ethyl-2-chloromethylpyrrolidine.

Discussion Of Results

The synthesis of 1-methyl-2-ethyl-3-piperidone was accomplished by methods similar to those used for analogous compounds (3,5).

When subjected to the Clemmensen reduction this aminoketone underwent rearrangement, being converted to 1-methyl-2-propylpyrrolidine. This product was identified by boiling point, density, refractive index, and melting point of derivatives, all of which correspond well to values reported in the literature. An authentic sample, prepared by reductive cyclization of methyl γ-nitroheptanoate, had properties identical with those of the product of the Clemmensen reduction.

Catalytic reduction or sodium-ethanol reduction of 1-methyl-2-ethyl-3-piperidone yielded 1-methyl-2-ethyl-3-hydroxypiperidine. This hydroxy compound, however, was not changed by subjection to the Clemmensen reduction. An attempt to prepare the corresponding 3-chloro-compound was unsuccessful.

The Clemmensen reduction of 1-methyl-2-propionyl-pyrrolidine resulted in the formation of the corresponding carbinol, in which the ring structure was unchanged.

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VITA

The author was born in Malcolm, Nebraska, on February 20, 1920. He attended the public schools in Aurora, Nebraska, and Lincoln, Nebraska, and was graduated from Jackson High School in Lincoln in 1938. He entered the University of Nebraska in 1938 and received the degree of Bachelor of Arts in 1942, and the degree of Master of Arts in 1943 from that institution. After serving in the United States Naval Reserve from 1943 to 1946, he entered the Graduate College of the University of Ilinois in the summer of 1946 with an appointment as part time teaching assistant. During the first semester of 1948-1949 he held a University Fellowship.

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